

Nanosuspension Loaded Oral Films: A Breakthrough Approach

Anu Mathew*, Susan Jacob, Shyma M.S

Department of Pharmaceutics, Mar Dioscorus College of Pharmacy, Alathara, Sreekaryam, Thiruvananthapuram, Kerala, India

Abstract

Nanotechnology-based techniques are widely used in pharmaceuticals for improving the solubility of poorly water-soluble drugs. The oral film containing nanoparticles was developed with the aim to transform nanosuspensions into solid dosage form and thereby increasing oral bioavailability of drugs. Nanosuspensions can be prepared by various methods such as high shear homogenization, solvent evaporation, and then lyophilized to get nanoparticles. These nanoparticles get incorporated in the oral film by mixing it with HPMC E15 or HPMC E5 and PEG 400 by the process of solvent casting.

Key words: Homogenization, nanosuspension, oral films, solvent casting

INTRODUCTION

Oral administration is the most preferred route due to its several advantages such as patient compliance, ease of administration, pain reduction, to accommodate various drug candidates. Geriatric & pediatric patients have problems in swallowing of oral solid dosage forms such as tablets & capsules.^[1] In these cases, fast dissolving drug delivery is a promising approach to increase patient compliance. These oral films undergo rapid disintegration and can be self-administered without swallowing and chewing. The oral films are flexible, more pliable & easily handled when compared to other oral dosage forms. These are dissolved to dissolve within a few seconds without water or chewing. Oral films generally used for oral ulcers, sores, or teething. Drugs such as antihistamines, cough remedies, erectile dysfunction, nausea, pain can be incorporated.^[11] The incorporation of nanotechnology into oral films is a novel approach for stabilizing nanosuspensions. Nanosuspensions are thermodynamically unstable and undergo aggregation during storage. Various stabilizers like hydrophilic polymers surfactants are available for stabilizing nanosuspensions, but the efficiency of stabilizers is uncertain upon dissolution, pH changes, etc. Formulation of nano suspension results in the reduction of drug particles to nano range which leads to an increase in dissolution rate and enhances bioavailability.

NANOSUSPENSION

Nanosuspension is defined as a submicron colloidal dispersion of drug particles which are stabilized by action of surfactants. The particle-size distribution of solid particles in nanosuspensions is generally less than 1 micron an average particle size ranging between 200 and 600 nm.^[3] The reduction of the size of drug particles up to the submicron range leads to a significant increase in dissolution rate and therefore, enhances bioavailability. Nanosuspension can be delivered by the oral and non-oral route of administration such as parenteral route, ocular route, etc. It not only solves the problem of poor solubility and bioavailability improves drug safety and efficacy as the drug remains in a crystalline state. Nanosuspension

formulation approach is most suitable for the compound with high log P value, high melting point, and high dose and for the drugs that are insoluble both in water and in organic media.^[2]

Advantages

- Provides ease of manufacture and scale-up for large-scale production.
- Long-term physical stability due to the presence of stabilizers.
- Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.
- Rapid dissolution and tissue targeting can be achieved by IV route of administration.
- Reduction in tissue irritation in case of subcutaneous/intramuscular administration.
- Higher bioavailability in case of ocular administration and inhalation delivery
- Improvement in biological performance due to high dissolution rate and saturation solubility of the drug.^[3]

COMPONENTS

STABILIZERS

Stabilizer shows a vital role in the formulation of nanosuspensions. In the lack of suitable stabilizers, the high surface energy of nanosized particles can induce agglomeration of the drug crystals. The main objective of a stabilizer is to produce a physically stable formulation by providing steric or ionic barriers. The stabilizers wet the drug particles thoroughly, and avoid Ostwald's ripening and agglomeration of nanosuspensions. The type and amount of stabilizer have a definite effect on the physical stability and in-vivo behaviour of nanosuspensions. In some cases, a blend of stabilizers is required to achieve a stable nanosuspension. The drug-to-stabilizer ratio in the formulation may differ from 1:20 to 20:1 and should be examined for a specific case e.g. Cellulosics, Poloxamer,

Polysorbates, Lecithin and Povidone. [4]

- **SURFACTANTS**
Surfactants are incorporated to improve the dispersion by decreasing the interfacial tension. Besides they act as wetting or deflocculating agents e.g. Tween 80 and Span - 80 widely used surfactants
- **CO-SURFACTANTS**
The selection of co-surfactant is critical when using microemulsion to formulate nanosuspensions. Since co-surfactants can significantly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for particular microemulsion composition and on drug loading should be studied e.g. Transcutol, glycofurol, and Isopropanol safely used as co-surfactants.
- **OTHER ADDITIVES**
Additives depend either on the route of administration or the properties of the drug moiety. Commonly used additives in nanosuspension are buffers, salts, polyols, osmogent, cryoprotectant [3]

NEED OF NANOSUSPENSION

If a drug is poorly soluble in water following major issues will arise:

- Poor bioavailability.
- Failure to optimize lead compound selection based on efficacy and safety.
- Lack of dose response proportionality.
- Sub-optimal dosing.
- Need to use harsh excipients i.e. excessive use of co-solvents and other excipients.
- Need to use extreme basic or acidic conditions to enhance solubility [3,4]

Nanosuspension can be used as an effective method in mitigating these issues. They are also used as a formulation approach in case of drugs that are insoluble in both inorganic media and water instead of using lipidic systems.

PREPARATION TECHNIQUES

High pressure homogenization (Disso cubes)

Disso Cubes are engineered using piston-gap-type high-pressure homogenizers. This method is intended to prepare nanosuspension of many poorly water soluble drugs. Homogenization involves driving the suspension under pressure through a valve having a narrow aperture.. Before the homogenization process, it is necessary to form a pre-suspension of the micronized drug in a surfactant solution using high-speed stirrers. During the homogenization process, the drug suspension is pushed through the homogenization gap to obtain nano-sizing of the drug. [2,4]

Homogenization in non-aqueous media (Nanopure)

Nanopure is the technology in which suspension homogenized in water-free media or water mixture. In the disso cubes technology, the cavitation is the determining factor of the process. In contrast to water, oils and oily

fatty acids have a high boiling point and low vapour pressure. Hence the drop of static pressure will not be sufficient enough to initiate cavitations. In nanopure technology, "deep freeze" homogenization is the process of homogenizing a drug suspension in the non-aqueous media at 0°C or even below the freezing point. The results obtained were comparable to disso cubes & hence, can be used effectively for thermolabile substance at milder conditions. [2]

Precipitation or solvent anti-solvent precipitation/hydrogel method

In this method, the drug is first dissolved in a solvent and then this solution is mixed with a miscible anti-solvent in the presence of surfactants. When the drug solution is added rapidly to anti-solvent results in the super saturation of drug followed by the formation of ultrafine crystalline or amorphous drug solid materials. [5]

Compressed anti-solvent (PCA)

In PCA (compressed anti-solvent), supercritical carbon dioxide plays a role as anti-solvent. The solutions of the selected drug and stabilizer are introduced into a chamber, containing compressed CO₂, by atomization. Consequently, nanocrystals are produced after atomization of drug and stabilizer solutions into the chamber. [3]

Dry co-grinding

Nanosuspensions prepared by high pressure homogenization and media milling are wet grinding processes. Recently, nanosuspensions can be obtained by dry milling procedures. Various soluble polymers and copolymers such as PVP, Polyethylene glycol, Hydroxypropyl methylcellulose and cyclodextrin derivatives have been used. Dissolution of poorly water soluble drugs and physicochemical properties were improved by co-grinding because of progress in the surface polarity and conversion from a crystalline to an amorphous drug. Dry co-grinding can be carried out easily and can be conducted without organic solvents. The co-grinding technique can decrease particles to the submicron level and a stable amorphous solid can be gained. [2]

Emulsification-solvent evaporation technique:

In this process, the drug solution is prepared by emulsification process then add this solution in that solvent which is non solvent for the drug then evaporate the solvent. When the solvent is evaporated there is the formation of precipitates/crystals of the drug. Growth of the crystal can be controlled by using high shear forces using high-speed stirrer. [2, 6]

EVALUATION OF NANOSUSPENSION

Viscosity Measurement

Brookfield type rotary viscometer is used to determine the viscosity of lipid based formulations of several compositions at different shear rates at different temperatures. The sample room of the instrument must be maintained at 37°C by a thermo bath and the samples, for the measurement are to be immersed in it. [7]

Determination of saturation solubility of

nanosuspension formulation

Saturation solubility is defined as “the maximum quantity of a compound (solute) that can be dissolved in a certain quantity of a specific solvent at a specified temperature.”

Procedure

2 mg of drug loaded nanosuspension was suspended in 2ml of water, 0.1N HCl and pH 6.8 phosphate buffers and shaken at 37°C for 24 hrs. From this, nanosuspension was filled into centrifugation tube and centrifuged at 10,000 rpm for 15 mins after that sample was filtered through 0.22 µm membrane filters and the filtrate was diluted appropriately with solvents. Sample was analyzed spectrophotometrically using UV-Visible spectrophotometer at 235nm

pH Value

The pH value of aqueous formulation should be taken at a given temperature and only after settling equilibrium has been reached, in order to minimize “pH drift” and electrode surface coating with suspended particles. Electrolyte should not be added to the external phase of the formulation to stabilize the pH. [7]

Determination of drug content

The drug content was determined by calibration curve method Procedure

100 mg of nanosuspension was accurately weighed and dissolved into 100 ml of methanol followed by sonication and then filtrated through whatmann filter paper. The amount of drug was determined by UV-Visible spectrophotometer at 210nm. The sample was analyzed in triplicate and the drug content was calculated using the calibration curve in methanol. [7]

Measurement of Zeta potential

Zeta meter 3.0 + is used for measuring zeta potential which indicates physical stability of nanosuspensions. The measurements were performed in distilled water in triplicate with conductivity adjusted to 50 µS and field strength 75 V/cm. [8]

ORAL FILMS

Orally fast-dissolving film is novel drug delivery system for the oral delivery of the drugs. It was based on the technology of the transdermal patch. The delivery system comprises of a very thin oral strip, which is just placed on the patient’s tongue or any oral mucosal tissue, rapidly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then quickly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. [9]



Fig 1: Example of film

Table 1: Classification of oral films^[1]

Property	Mucoadhesive sustained release wafer	Flash release wafer	Mucoadhesive melt-away wafer
Area (cm ²)	2-4	2-8	2-7
Thickness (mm)	50-250	20-70	50-500
Structure	Multi-layer system	Single layer	Single or multilayer system
Drug phase	Suspension and/or solid solution	Solid solution	Solid solution or suspended drug particles
Application	Gingival, (other region in the oral cavity)	Tongue(upper palate)	Gingival or buccal Region
Dissolution	Maximum 8-10 hours	Maximum 60 seconds	Disintegration in a few minutes, forming gel
Site of action	Systemic or local	Systemic or local	Systemic or local

Advantages

- Due to its larger surface area, it gets rapidly dissolved & disintegrated in the oral cavity
- Rapid onset of action, efficacy
- More flexible & pliable
- Accurate dosing can be assured
- Easily handling and storage
- As compared to liquid formulations, accuracy in the administered dose is ensured from each strip of the film [10]

Disadvantages

- Cannot incorporate high doses
- Drugs which are unstable at buccal pH cannot be administered
- Taste masking is necessary in case of bitter drugs
- Special packaging is needed since oral thin films are fragile and must be protected from water [1]

Classification

- Flash release
- Mucoadhesive melt away water
- Mucoadhesive sustained
- Release wafers

FORMULATION CONSIDERATION

- **API**
Due to the limitation in the size of the dosage form, high doses couldn't be loaded. API can be micronized or milled & loaded in the form of nanocrystals or depend on the release profile. The selected API must stable in both saliva and water
- **Film-forming polymers**
Polymers can be used alone or in combination to obtain the desired film. It must be tough enough to prevent damage during handling and transportation. It must have the property to disintegrate within seconds when placed in the mouth. The film formed must be transparent and free of bubbles which are necessary for its aesthetic look
- **Plasticizers**
The major ingredient which helps to improve the flexibility & reduce the brittleness of strip. The compatibility with the polymer and the solvent type is the major criteria to be considered while selecting plasticizers. Commonly used plasticizers include Polyethylene glycol, Propylene glycol, phthalate derivatives, etc. Plasticizers improve the flow of polymer and increase its strength. The combination of HPMC E15 along with PEG 400 provide good film-forming cap and transparent appearance. [11]
- **Sweetening agents**
Sweetening agents become important constituent in the formulation which is intended to be disintegrated or dissolved in the oral cavity. Both natural and artificial sweeteners are used in fast-dissolving films. The concentration of sweetening agents of 3-6% in

combination or alone. Sucrose is the major source of sweeteners, but cannot be used in the case of diabetic patients. Artificial sweeteners include aspartame, cyclamate, sucralose, etc.

- **Saliva stimulating agent**

They are used to enhance the production of saliva which increases the disintegration of fast dissolving film in the mouth. Mainly includes citric acid, lactic acid, and ascorbic acid. Used in 2-6% of the weight of film. [1]

- **Flavoring agent**

The flavor should be selected by considering the type & quantity of the drug that is incorporated in the film. The color preference for young people is fruit punch, raspberry and lemon, orange for geriatric use. Peppermint oil, cinnamon oil, nutmeg oil are examples of flavor oils.

- **Coloring agent**

FD&C approved color should be used in oral films.

Titanium dioxide is a commonly used coloring agent. [10]

METHOD OF PREPARATION

The following process can be used to prepare mouth dissolving film

- Solvent casting method
- Semisolid casting
- Hot-melt extrusion
- Rolling

Solvent casting method

Solvent casting is the most generally used method for the preparation of oral films using water soluble excipients, polymers and drug which are dissolved in de-ionized water. As a result, homogenous mixture is obtained by applying high shear forces produced by a shear processor. Then, the prepared solution is transferred onto petri plate and the solvent is allowed to dry by exposing it to high temperature in order to obtain good quality films. [12]

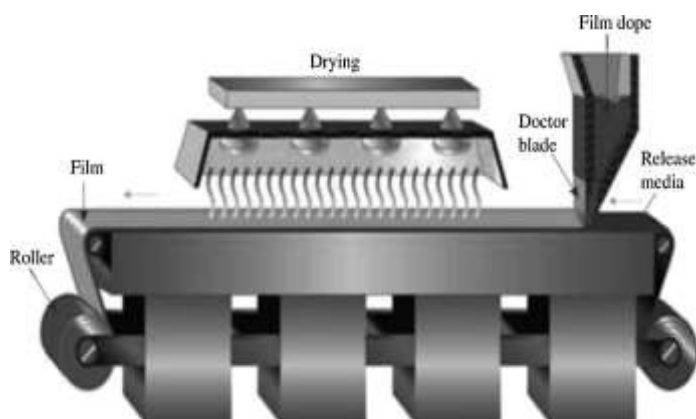


Fig: 2 solvent casting method [12]

Semisolid casting

In this method firstly a solution of water soluble film polymer is prepared and this solution is added to acid

insoluble polymer solution, which is prepared in ammonium or sodium hydroxide. To form a gel mass, an appropriate amount of plasticizer is added, then cast to films. The ratio between acid insoluble polymer to film forming polymer should be 1:4. [10]

Hot melt extrusion

In this method, the drug is taken along with carrier in solid form. Then pass through extruder having heaters which melt the mixture. Finally, the melt is shaped to films by using dies. Then dried granular material is introduced into the extruder. To process the granules inside the barrel of the extruder, the screw speed should be set at 15 rpm. The processing temperatures should be 800C (zone 1), 1150C (zone 2), 1000C (zone 3) and 650C (zone 4). Finally, to obtain the film, the extrudate (T = 650C) is pressed into a cylindrical calendar. [10]

Rolling method

This method involves the preparation of premix by the addition of active ingredient and subsequent formation of film. The pre-mix batch include film forming polymer, polar solvent and other ingredients except active ingredient added to the master batch feed tank. Then a fixed amount of the master batch is fed by using a metering pump and control valve. The desired amount of drug is added into the mixer and then blended for a sufficient time to form a homogenized matrix. A precise amount of matrix is fed into the pan through a second metering pump. The metering roller determined the thickness of the film. Finally, the film is formed on the substrate and taken by means of support roller. The wet is dried by using controlled bottom drying. [11]

FORMULATION OF ORAL FILM LOADED NANOSUSPENSION

Oral thin films of optimized nanosuspension were prepared by solvent casting method. The accurately weighed quantities of polymers such as HPMC, PEG were added to nanosuspension formulation (equivalent to weight of drug) and stirred using a magnetic stirrer for 30 min. The final mixture was then casted on a petriplate and dried in hot air oven for 2 hour at 50°C. After drying the films were removed with the help of the sharp blade, cut in suitable sizes and packed in aluminium foil and kept in a desiccator till further evaluation. [13]

EVALUATIONS

Weight Uniformity: Films can be weighed on an analytical balance and average weight can be determined for each film. It is useful to ensure that a film contains a proper amount of excipients and drugs. [1]

Thickness:

The thickness of the film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of the dose in the film. [14]

Particle size distribution and polydispersity index:

Particle size was determined using Photon correlation spectroscopy using Horiba Nanoparticle Analyser. This analysis yields the mean particle diameter (z-average), Polydispersity index, and zeta potential at 25 °C. [13]

Dryness Test/Tack Tests:

About eight stages of film drying process have been identified and they are set-to touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat dry print free. Tack is defined as the tenacity with which the strip adheres to an accessory that has been pressed into contact with the strip. Instruments are also available for this study. [1]

Surface pH:

The surface pH of fast dissolving films was determined in order to investigate the possibility of any side effects in vivo. The films were allowed to swell in closed petridish at room temperature for 30 minutes in 5ml of distilled water. Solution was placed under digital pH meter. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation. [12, 15]

Contact Angle:

Goniometer determined the contact angle at room temperature. Put a drop of double distilled water on the dry film surface. Image of water droplet recorded within 10sec of deposition by using a digital camera. To determine angle, analyze the digital picture. The contact angle was measured on both side of the drop and averaged. [12]

Folding endurance:

Used to estimate mechanical properties of the film. The ability of patch to withstand rupture is termed as folding endurance. Higher the value of folding endurance lower was chance of film to rupture easily and vice versa. It was determined by repeatedly folding a small strip of film of 2×2 cm² at the same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave value of folding endurance. High folding endurance determines the higher mechanical strength of the film. [12]

Disintegration time:

For fast disintegrating oral films, the disintegrating time limit of 30 sec or less can be employed. However still no official guideline is available for oral strips, this may be used as a qualitative guideline for quality control test. Generally, disintegration time for the oral strip is 5-30sec.

In-vitro drug release:

The dissolution study was carried out using USP basket dissolution apparatus. The dissolution was carried out at pH 6.8 in 900 ml of phosphate buffer maintained at 37 ± 0.5°C at 50 rpm. The samples were taken at various time intervals and replaced with fresh buffer (pH 6.8). The samples were filtered through whatman filter paper, diluted with buffer and analyzed by UV spectrophotometer at 241nm. [17]

Table 2: Marketed fast dissolving films [10,11]

PRODUCT	API	MANUFACTURER	USE
Benadryl	Diphenhydramine HCl	Pfizer	Antiallergic
Theraflu	Dextromethorphan	Novartis	Antiallergic
Oragel	Menthol	Del	Mouth freshner
Suppress	Menthol	Innozen, Inc.	Cough supressent
Sudated PE	Phenylepinephrine	Wolters health, Inc.	Kluwer Congestion

Assay/drug content and content uniformity:

For checking assay/drug content, any standard assay method described for the particular API in any of the standard pharmacopoeia can be used. Content uniformity is determined by assessing the API content in an individual strip. The limit of content uniformity is 85–115 percent. [12]

Organoleptic evaluation

For evaluation of the psychophysical evaluation of the product, special controlled human taste panels are used. For this purpose, in-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods can be used. These in-vitro taste assessment apparatus and methods are well suited for taste screening of oral pharmaceutical formulations. [1]

CONCLUSION

Nanosuspensions are unique and commercially feasible approach to resolve the problems of hydrophobic drug such as poor solubility and poor bioavailability. As nanosuspensions are prone to destabilization by agglomeration, oral films can be used as a novel approach for stabilization through solidification of optimized nanosuspension. The conversion of nanosuspension into OTF formulation helps to retain the particle size in nano size. The fast dissolving thin film is hardly defined, but seem to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the good applicability of a liquid and the greater stability of a solid dosage form. Production techniques such as media milling and high-pressure homogenization have been effectively employed for large-scale production of nanosuspensions. Formulation of films with suitable physical-mechanical properties containing nanoparticles in one formulation step is possible. [16] Both the film and the nanoparticle properties were dependent on the components used in the formulation

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